

10D16

SEARCH REQUEST FORM

Requestor's Name: Dr J Sehoratayun Serial Number: 09/832,659
Date: 7/1/02 Phone: 305-3112 Art Unit: 1647

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Inventors: Adrian Whitty,
Laura Runcel
Morgot Brickelmayer
Paula Hochman.

Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

Claims 1-9, 28, 29 and 31.

These claims are related to polypeptide sequences with glycosylated interferon - B.

X - Y - Z
|
(IFB) linker → polypeptide open
muc int. B.

Earliest date 10/16/98.

Claims are checked.

Thanks

By

Ifn-β fusion proteins

STAFF USE ONLY

Date completed: 7-9-02
Searcher: prSB
Terminal time: 43
Elapsed time: prep 26
CPU time: _____
Total time: _____
Number of Searches: _____
Number of Databases: _____

Search Site	Vendors
STIC	IG
CM-1	191 STN
Pre-S	Dialog
N.A. Sequence	APS
A.A. Sequence	Geninfo
Structure	SDC
Bibliographic	DARC/Questel
	Other

=> fil capl
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FILE COVERS 1907 - 9 Jul 2002 VOL 137 ISS 2
FILE LAST UPDATED: 8 Jul 2002 (20020708/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d que 18; d que 116; d que 118

L5 8013 SEA FILE=CAPLUS ABB=ON INTERFERON#/OBI(L)BETA
L6 86620 SEA FILE=CAPLUS ABB=ON IMMUNOGLOBULIN#/OBI
L7 136243 SEA FILE=CAPLUS ABB=ON (FUSION OR CHIMER? OR CHIMAER?) /OBI
L8 6 SEA FILE=CAPLUS ABB=ON L5(L)L6(L)L7

L5 8013 SEA FILE=CAPLUS ABB=ON INTERFERON#/OBI(L)BETA
L6 86620 SEA FILE=CAPLUS ABB=ON IMMUNOGLOBULIN#/OBI
L7 136243 SEA FILE=CAPLUS ABB=ON (FUSION OR CHIMER? OR CHIMAER?) /OBI
L13 33606 SEA FILE=CAPLUS ABB=ON GLYCOSYLAT?
L14 13 SEA FILE=CAPLUS ABB=ON POLYALKYLGlyCOL#
L15 3552 SEA FILE=CAPLUS ABB=ON POLYALKYL?(L)GLYCOL#/OBI
L16 3 SEA FILE=CAPLUS ABB=ON L5 AND L6 AND L7 AND (L13 OR L14 OR L15)

L5 8013 SEA FILE=CAPLUS ABB=ON INTERFERON#/OBI(L)BETA
L7 136243 SEA FILE=CAPLUS ABB=ON (FUSION OR CHIMER? OR CHIMAER?) /OBI
L14 13 SEA FILE=CAPLUS ABB=ON POLYALKYLGlyCOL#
L15 3552 SEA FILE=CAPLUS ABB=ON POLYALKYL?(L)GLYCOL#/OBI
L18 1 SEA FILE=CAPLUS ABB=ON (L14 OR L15) AND L5 AND L7

=> s 18 or 116 or 118

L92 9 L8 OR L16 OR L18

=> fil wpids

FILE 'WPIDS' ENTERED AT 14:05:44 ON 09 JUL 2002
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FILE LAST UPDATED: 04 JUL 2002 <20020704/UP>
MOST RECENT DERWENT UPDATE 200242 <200242/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> Update 2002-42 does not contain any new polymer indexing <<<

>>> The BATCH option for structure searches has been
enabled in WPINDEX/WPIDS and WPIX >>>

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
SEE [<<<](http://www.derwent.com/dwpi/updates/dwpicov/index.html)

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:

[<<<](http://www.stn-international.de/training_center/patents/stn_guide.pdf)

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:

[<<<](http://www.derwent.com/userguides/dwpi_guide.html)

=> d que 124; d que 126; d que 129

L20 611 SEA FILE=WPIDS ABB=ON INTERFERON#(3A)BETA
L21 6993 SEA FILE=WPIDS ABB=ON IMMUNOGLOBULIN# OR IMMUNO GLOBULIN#
L22 38461 SEA FILE=WPIDS ABB=ON FUSION OR CHIMER? OR CHIMAER?
L24 6 SEA FILE=WPIDS ABB=ON L20 (S) L21 (S) L22

L20 611 SEA FILE=WPIDS ABB=ON INTERFERON#(3A)BETA
L22 38461 SEA FILE=WPIDS ABB=ON FUSION OR CHIMER? OR CHIMAER?
L25 72 SEA FILE=WPIDS ABB=ON L20(3A) (1A OR 1 A)
L26 5 SEA FILE=WPIDS ABB=ON L25 AND L22

L20 611 SEA FILE=WPIDS ABB=ON INTERFERON#(3A)BETA
L22 38461 SEA FILE=WPIDS ABB=ON FUSION OR CHIMER? OR CHIMAER?
L27 1852 SEA FILE=WPIDS ABB=ON GLYCOSYLAT?
L28 5854 SEA FILE=WPIDS ABB=ON POLYALKYLGLYCOL? OR (POLY ALKYL? OR
POLYALKYL?) (W)GLYCOL# OR POLY(W) (ALKYLGLYCOL? OR ALKYLENEGLYCO
L#) OR POLYALKYLENEGLYCOL#
L29 5 SEA FILE=WPIDS ABB=ON L20 AND L22 AND (L27 OR L28)

=> s 124 or 126 or 129

L93 10 L24 OR L26 OR L29

=> fil biotechno

FILE 'BIOTECHNO' ENTERED AT 14:05:47 ON 09 JUL 2002
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FILE LAST UPDATED: 05 JUL 2002 <20020705/UP>
FILE COVERS 1980 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
/CT AND BASIC INDEX <<<

=> d que 137;d que 149; s 137 or 149

L31	4677 SEA FILE=BIOTECHNO ABB=ON	INTERFERON(3A)BETA
L33	51361 SEA FILE=BIOTECHNO ABB=ON	FUSION OR CHIMER? OR CHIMAER?
L34	2 SEA FILE=BIOTECHNO ABB=ON	POLYALKYLGlyCOL? OR (POLY ALKYL? OR POLYALKYL?) (W)GLYCOL# OR POLY(W) (ALKYLGLYCOL? OR ALKYLENEGLYCO L#) OR POLYALKYLENEGLYCOL#
L35	15288 SEA FILE=BIOTECHNO ABB=ON	GLYCOSYLAT?
L37	2 SEA FILE=BIOTECHNO ABB=ON	L31 AND (L34 OR L35) AND L33

L40	2565 SEA FILE=BIOTECHNO ABB=ON	BETA INTERFERON/CT
L42	2294 SEA FILE=BIOTECHNO ABB=ON	CHIMERIC PROTEIN/CT
L43	5982 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN/CT
L44	5158 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN A/CT
L45	8341 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN M/CT
L46	14798 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN G/CT
L47	616 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN D/CT
L48	5384 SEA FILE=BIOTECHNO ABB=ON	IMMUNOGLOBULIN E/CT
L49	1 SEA FILE=BIOTECHNO ABB=ON	L40 AND L42 AND (L43 OR L44 OR L45 OR L46 OR L47 OR L48)

L94 3 L37 OR L49

=> fil biosis

FILE 'BIOSIS' ENTERED AT 14:05:50 ON 09 JUL 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 3 July 2002 (20020703/ED)

=> d que 160; d que 165;d que 167

L56	8568 SEA FILE=BIOSIS ABB=ON	BETA(3A) (INTERFERON# OR IFN)
L58	101196 SEA FILE=BIOSIS ABB=ON	FUSION OR CHIMER? OR CHIMAER?
L59	273 SEA FILE=BIOSIS ABB=ON	L56(3A)(1A OR 1 A)
L60	2 SEA FILE=BIOSIS ABB=ON	L59 AND L58

L56	8568 SEA FILE=BIOSIS ABB=ON	BETA(3A) (INTERFERON# OR IFN)
L57	150451 SEA FILE=BIOSIS ABB=ON	IMMUNOGLOBULIN#
L58	101196 SEA FILE=BIOSIS ABB=ON	FUSION OR CHIMER? OR CHIMAER?
L64	154609 SEA FILE=BIOSIS ABB=ON	IG#
L65	6 SEA FILE=BIOSIS ABB=ON	L56(S) (L57 OR L64) (S)L58

L56	8568 SEA FILE=BIOSIS ABB=ON	BETA(3A) (INTERFERON# OR IFN)
L58	101196 SEA FILE=BIOSIS ABB=ON	FUSION OR CHIMER? OR CHIMAER?
L61	30524 SEA FILE=BIOSIS ABB=ON	GLYCOSYLAT?
L62	42 SEA FILE=BIOSIS ABB=ON	POLYALKYLGlyCOL? OR (POLY ALKYL? OR POLYALKYL?) (W)GLYCOL# OR POLY(W) (ALKYLGLYCOL? OR ALKYLENEGLYCO L#) OR POLYALKYLENEGLYCOL#
L67	4 SEA FILE=BIOSIS ABB=ON	L56 AND L58 AND (L61 OR L62)

=> s 160 or 165 or 167

L95 12 L60 OR L65 OR L67

=> fil embase

FILE 'EMBASE' ENTERED AT 14:05:52 ON 09 JUL 2002
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FILE COVERS 1974 TO 8 Jul 2002 (20020708/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que 177; d que 180; d que 182

L68 653 SEA FILE=EMBASE ABB=ON BETA1A INTERFERON/CT
L76 14516 SEA FILE=EMBASE ABB=ON RECOMBINANT PROTEIN/CT OR CHIMERIC
PROTEIN/CT
L77 5 SEA FILE=EMBASE ABB=ON L68 AND L76

L69 5499 SEA FILE=EMBASE ABB=ON BETA INTERFERON/CT
L72 28864 SEA FILE=EMBASE ABB=ON GLYCOSYLAT?
L73 7 SEA FILE=EMBASE ABB=ON POLYALKYLGlyCOL? OR (POLY ALKYL? OR
POLYALKYL?) (W) GLYCOL# OR POLY(W) (ALKYLGlyCOL? OR ALKYLENEGLYCO
L#) OR POLYALKYLENEGLYCOL#
L76 14516 SEA FILE=EMBASE ABB=ON RECOMBINANT PROTEIN/CT OR CHIMERIC
PROTEIN/CT
L80 1 SEA FILE=EMBASE ABB=ON L69 AND L76 AND (L72 OR L73)

L69 5499 SEA FILE=EMBASE ABB=ON BETA INTERFERON/CT
L71 129822 SEA FILE=EMBASE ABB=ON IMMUNOGLOBULIN+NT/CT
L76 14516 SEA FILE=EMBASE ABB=ON RECOMBINANT PROTEIN/CT OR CHIMERIC
PROTEIN/CT
L82 3 SEA FILE=EMBASE ABB=ON L69 AND L76 AND L71

=> s 177 or 180 or 182

L96 9 L77 OR L80 OR L82

=> fil medl

FILE 'MEDLINE' ENTERED AT 14:05:55 ON 09 JUL 2002

FILE LAST UPDATED: 7 JUL 2002 (20020707/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d que 189; d que 190; d que 191

L83 2326 SEA FILE=MEDLINE ABB=ON INTERFERON-BETA/CT
L85 39983 SEA FILE=MEDLINE ABB=ON RECOMBINANT FUSION PROTEINS+NT/CT
L88 44180 SEA FILE=MEDLINE ABB=ON 1A OR 1 A
L89 1 SEA FILE=MEDLINE ABB=ON L83 AND L88 AND L85

L83 2326 SEA FILE=MEDLINE ABB=ON INTERFERON-BETA/CT
L85 39983 SEA FILE=MEDLINE ABB=ON RECOMBINANT FUSION PROTEINS+NT/CT
L86 35990 SEA FILE=MEDLINE ABB=ON GLYCOSYLAT?
L87 4 SEA FILE=MEDLINE ABB=ON POLYALKYLGLYCOL? OR (POLY ALKYL? OR
POLYALKYL?) (W) GLYCOL# OR POLY(W) (ALKYLGLYCOL? OR ALKYLENEGLYCO
L#) OR POLYALKYLENEGLYCOL#
L90 0 SEA FILE=MEDLINE ABB=ON L83 AND L85 AND (L86 OR L87)

L83 2326 SEA FILE=MEDLINE ABB=ON INTERFERON-BETA/CT
L84 170775 SEA FILE=MEDLINE ABB=ON IMMUNOGLOBULINS+NT/CT
L85 39983 SEA FILE=MEDLINE ABB=ON RECOMBINANT FUSION PROTEINS+NT/CT
L91 0 SEA FILE=MEDLINE ABB=ON L83 AND L85 AND L84

=> dup rem 189,192,195,194,196,193
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PROCESSING COMPLETED FOR L92
PROCESSING COMPLETED FOR L95
PROCESSING COMPLETED FOR L94
PROCESSING COMPLETED FOR L96
PROCESSING COMPLETED FOR L93
L97 38 DUP REM L89 L92 L95 L94 L96 L93 (6 DUPLICATES REMOVED)
ANSWER '1' FROM FILE MEDLINE
ANSWERS '2-10' FROM FILE CAPLUS
ANSWERS '11-22' FROM FILE BIOSIS
ANSWER '23' FROM FILE BIOTECHNO
ANSWERS '24-31' FROM FILE EMBASE
ANSWERS '32-38' FROM FILE WPIDS

=> d ibib ab 1-38; fil hom

L97 ANSWER 1 OF 38 MEDLINE
ACCESSION NUMBER: 2002157053 MEDLINE
DOCUMENT NUMBER: 21885918 PubMed ID: 11888675

TITLE: Abrogation of IRF-1 response by high-risk HPV E7 protein in vivo.
 AUTHOR: Um Soo-Jong; Rhyu Jae-Woong; Kim Eun-Joo; Jeon Kook-Che;
 Hwang Eun-Seoung; Park Jong-Sup
 CORPORATE SOURCE: Department of Bioscience and Biotechnology/Institute of Bioscience, Sejong University, Seoul, South Korea.
 SOURCE: CANCER LETTERS, (2002 May 28) 179 (2) 205-12.
 Journal code: 7600053. ISSN: 0304-3835.
 PUB. COUNTRY: Ireland
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200206
 ENTRY DATE: Entered STN: 20020313
 Last Updated on STN: 20020612
 Entered Medline: 20020611

AB We have previously reported that human papillomavirus (HPV) E7 interacts with IRF-1, a key regulator of cellular immune response, and abrogates its transactivation function at the molecular level in vitro. To confirm our previous data, we investigated in vivo the E7-mediated down-regulation of IRF-1 using HPV E7-inducible cells and transgenic mice expressing HPV-18 E6/E7. When E7 was induced in the absence of tetracycline, the expression of target genes of IRF-1 (TAP-1, IFN-beta, MCP-1 that are important for cellular immunity) was clearly reduced as determined by RT-PCR. In addition, the IRF-1 activity was down-regulated in E7-expressing cells into which IFN-beta-CAT reporter plasmid was transfected. To further investigate the E7-mediated immune regulation in vivo, we constructed transgenic mice expressing E6 and E7 genes of HPV-18 under the control of HPV-18 promoter (URR). From several rounds of breeding, we obtained from a transgenic line that developed a cervical dysplasia and expressed E6/E7 as determined by histological examination and RT-PCR, respectively. Subsequent RT-PCR analysis indicated that TAP-1, IFN-beta, and MCP-1 genes were less expressed in a cervical tissue derived from transgenic mouse, when compared with a cervix derived from normal mouse. From these results, we conclude that the E7 transgene expression inactivates the transactivation function of IRF-1 in vivo, which might be important for the elucidation of the E7-mediated immune evading mechanism that is frequently found in cervical cancer.

L97 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
 ACCESSION NUMBER: 2001:300891 CAPLUS
 DOCUMENT NUMBER: 134:322353
 TITLE: Post-translational modification of recombinant proteins in plants by altering its natural modification abilities
 INVENTOR(S): Russell, Douglas; Manjunath, Siva; Bassuner, Ronald
 PATENT ASSIGNEE(S): Monsanto Company, USA
 SOURCE: PCT Int. Appl., 132 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029242	A2	20010426	WO 2000-US29027	20001020
WO 2001029242	A3	20020221		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,				

ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-160758P P 19991021
 US 2000-195282P P 20000407

AB The present invention is directed to methods for producing a post-translationally modified heterologous polypeptide in a plant host system by altering the natural post-translational abilities of that plant host system. The post-translational modification may be proteolytic cleavage, glycosylation, phosphorylation, methylation, sulfation, prenylation, acetylation, N-amidation, oxidn., hydroxylation, or myristylation. In a preferred embodiment, this method includes transforming a plant host system with a nucleic acid that encodes a heterologous polypeptide, and isolating that polypeptide from the plant host system. The heterologous proteins may include antibodies and antibody fragments, collagen types I-XX, human protein C, and cytokines. In another aspect of this method, altering the natural post-translational modifications is done by transforming the plant host system with one or more nucleic acid sequences encoding a post-translational modification enzyme. Such plant specific post-translational modifying enzymes include Galactosyl transferase, xylosyl transferase, and fucosyl transferase. In an alternative aspect, the altering is done by mutagenesis of plant host system. In another embodiment, the altering is done by transforming said plant host system with an expression vector comprising a nucleic acid sequence that encodes an antisense nucleic acid. The invention further provides a method for producing a post-translationally modified heterologous polypeptide in a plant host system, by cross-pollinating a first plant, wherein the plant has been transformed with a first expression vector comprising a nucleic acid sequence encoding a heterologous polypeptide, and a second plant wherein the second plant has been transformed with a second expression vector comprising a nucleic acid sequence encoding a post-translational modifying enzyme.

L97 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

ACCESSION NUMBER: 2001:50519 CAPLUS

DOCUMENT NUMBER: 134:130268

TITLE: Immunoglobulin fusion proteins

INVENTOR(S): Cox, George N., III; Doherty, Daniel H.

PATENT ASSIGNEE(S): Bolder Biotechnology Inc., USA

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001003737	A1	20010118	WO 2000-US19336	20000713
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1200124	A1	20020502	EP 2000-947408	20000713
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			

PRIORITY APPLN. INFO.: US 1999-143458P P 19990713

WO 2000-US19336 W 20000713

AB The present invention relates to novel methods for making fusion proteins comprising a cytokine or growth factor fused to an Ig domain. The growth factor/cytokine can be fused directly to an Ig domain or through a peptide linker. The purified growth factor/cytokine-IgG fusion proteins produced by the novel methods are biol. active and can be used to treat diseases for which the non-fused growth factor/cytokine are useful.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
 ACCESSION NUMBER: 2000:278008 CAPLUS
 DOCUMENT NUMBER: 132:320955
 TITLE: Interferon-beta fusion proteins and uses
 INVENTOR(S): Whitty, Adrian; Runkel, Laura; Brickelmaier, Margot;
 Hochman, Paula
 PATENT ASSIGNEE(S): Biogen, Inc., USA
 SOURCE: PCT Int. Appl., 82 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000023472	A2	20000427	WO 1999-US24200	19991015
WO 2000023472	A3	20000831		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1121382	A2	20010808	EP 1999-956574	19991015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9915548	A	20010814	BR 1999-15548	19991015
NO 2001001861	A	20010613	NO 2001-1861	20010411
PRIORITY APPLN. INFO.:			US 1998-104491P P	19981016
			US 1999-120237P P	19990216
			WO 1999-US24200 W	19991015

AB A fusion polypeptide is described having the amino acid sequence X-Y-Z, or portion thereof, comprising the amino acid sequence of a glycosylated interferon-.beta. (X); Y is an optional linker moiety; and Z is a polypeptide comprising at least a portion of a polypeptide other than glycosylated interferon-.beta.. It is preferred that X is a human interferon-.beta.-1a, and Z is the const. region of an Ig of the class selected from IgM, IgG, IgD, IgA, and IgE. Mutants of interferon-.beta.-1a are also described. The fusion proteins are capable of inhibiting angiogenesis or neovascularization and are useful for treating multiple sclerosis, fibrosis, inflammatory or autoimmune diseases, cancers, hepatitis and other viral diseases.

L97 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2001:489516 CAPLUS
 DOCUMENT NUMBER: 135:87194
 TITLE: Branched polyalkylene glycols
 INVENTOR(S): Yamasaki, Motoo; Suzawa, Toshiyuki; Murakami, Tatsuya;

PATENT ASSIGNEE(S): Sakurai, Noriko; Yamashita, Kinya; Mukai, Mayumi;
 Kuwabara, Takashi; Ohta, So; Miki, Ichiro
 SOURCE: Kyowa Hakko Kogyo Co., Ltd., Japan
 PCT Int. Appl., 103 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001048052	A1	20010705	WO 2000-JP9159	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: JP 1999-366312 A 19991224

AB Branched polyalkylene glycols useful as reagents for chem. modifying physiol. active polypeptides wherein two single-chain polyalkylene glycols are attached to a group having a cyclic structure other than a planar structure and a group reactive with an amino acid side chain, the N-terminal amino group or the C-terminal carboxyl group in a polypeptide or a group which can be converted into such a reactive group is further attached thereto.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:573937 CAPLUS
 DOCUMENT NUMBER: 133:172593
 TITLE: Glycosylated leptin mutant compositions with improved pharmacokinetic properties
 INVENTOR(S): Martin, Frances H.; Elliott, Steven G.
 PATENT ASSIGNEE(S): Amgen Inc., USA
 SOURCE: PCT Int. Appl., 164 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047741	A1	20000817	WO 2000-US3652	20000211
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1151102	A1	20011107	EP 2000-911784	20000211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-249675 A 19990212

WO 2000-US3652 W 20000211

AB The present invention relates to **glycosylated** leptin compns. and related methods. Included are **glycosylated** leptin proteins having a Stokes' radius allowing for improved properties, as well as **glycosylated** leptin proteins having selected sites for **glycosylation**, nucleic acids encoding such proteins, related host cells, vectors, processes for prodn., and methods of use of such compns. The **glycosylated** leptins have longer systemic circulation times in vivo, without toxicities. Further, the biol. activity is equal to or slightly more potent than recombinant human native leptin protein. Novel methods of producing **glycosylated** proteins are also provided. The **glycosylated** leptin protein can be used for prep. a pharmaceutical compn. that can be used in the treatment of a human for a condition selected among obesity, diabetes, and high blood lipid content.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:354301 CAPLUS

DOCUMENT NUMBER: 131:4242

TITLE: **Interferon-.beta. fusion**INVENTOR(S): protein with **immunoglobulin Fc fragment**

Chang, Tse Wen; Yu, Liming

PATENT ASSIGNEE(S): Tanox, Inc., USA

SOURCE: U.S., 7 pp., Cont.-in-part of U.S. 5,723,125.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5908626	A	19990601	US 1997-994719	19971219
US 5723125	A	19980303	US 1996-719331	19960925
PRIORITY APPLN. INFO.:			US 1995-579211	19951228
			US 1996-719331	19960925

AB The authors disclose a hybrid recombinant protein consisting of human interferon-.beta. and an Ig Fc fragment (preferably .gamma.4 chain) joined by a peptide linker. The hybrid mol. has increased circulatory half-life.

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L97 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:667965 CAPLUS

DOCUMENT NUMBER: 129:299458

TITLE: Cloning and cDNA sequences of human interferon .alpha./.beta.-binding proteins I and II and their pharmaceutical uses

INVENTOR(S): Novick, Daniela; Cohen, Batya; Rubinstein, Menachem

PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd., Israel

SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 115,741, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5821078	A	19981013	US 1995-385191	19950207
PRIORITY APPLN. INFO.:			IL 1992-103052	A 19920903

IL 1993-106591 A 19930804
 US 1993-115741 B2 19930903
 IL 1994-108584 A 19940207

AB Interferon .alpha./.beta. binding proteins are provided, which are capable of modulating the activity of interferon-.alpha. subtypes as well as interferon-.beta.. Cloning of DNA mols. encoding these proteins, expression in host cells and antibodies against the proteins are also provided. Type I interferons (IFN-.alpha. and IFN-.beta. and IFN-.omega.) are a family of cytokines usually defined by their ability to confer resistance to viral infections. There are pathol. situations, related to these cytokines where neutralization of interferon activity may be beneficial to the patient. Cytokine-binding proteins (sol. cytokine receptors) correspond to the extracellular ligand binding domains of their resp. cell surface cytokine receptors. They are derived either by alternative splicing of pre-mRNA common to the cell surface receptor, or by proteolytic cleavage of the cell surface receptor. Therefore interferon .alpha./.beta. binding proteins were targeted that are capable of modulating the activity of interferon-.alpha. subtypes as well as interferon-.beta..

L97 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:808071 CAPLUS
 DOCUMENT NUMBER: 123:225960
 TITLE: The .beta.-subunit of mammalian interferon .gamma.
 receptors and cDNAs encoding them and their uses
 INVENTOR(S): Aguet, Michel; Boehni, Ruth; Hemmi, Silvio
 PATENT ASSIGNEE(S): USA
 SOURCE: PCT Int. Appl., 84 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516036	A2	19950615	WO 1994-US14277	19941207
WO 9516036	A3	19950831		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2177471	AA	19950615	CA 1994-2177471	19941207
EP 733111	A1	19960925	EP 1995-908418	19941207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1993-164596	19931209
			WO 1994-US14277	19941207

AB Novel transmembrane proteins that belong to the interferon receptor family and which are species-specific cofactors needed for signal transduction of interferon-.gamma. (IFN-.gamma.) and cDNAs encoding them are described. The .beta. subunit appears to be a component of a no. of other related receptors, e.g. for interleukins, erythropoietin and interferons .alpha. and .beta. and so the protein or an antagonist may be of therapeutic use (no data). The mouse cDNA was cloned by expression in COSN31 cells using a cDNA library from early B cells in pAGS3. Cells expressing the cDNA were induced to synthesize the tac antigen by exposure to IFN-.gamma. and antibody selection of tac-pos. cells. The transcript was found in spleen, liver, kidney, lung, and brain and appears to be the product of a single gene. A corresponding human cDNA was cloned by heterologous probing and the gene found to map to chromosome 21.

L97 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:77809 CAPLUS
 DOCUMENT NUMBER: 116:77809
 TITLE: Recombinant soluble interferon receptors and their use

INVENTOR(S): in diagnosis and pharmaceuticals
 Eid, Pierre; Gresser, Ion; Lutfalla, Georges; Meyer,
 Francois; Mogensen, Knud Erik; Tovey, Michael G.; Uze,
 Gilles

PATENT ASSIGNEE(S): Laboratoire Europeen de Biotechnologie, Fr.

SOURCE: Fr. Demande, 52 pp.

CODEN: FRXXBL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2657881	A1	19910809	FR 1990-1298	19900205
FR 2657881	B1	19940819		
CA 2085469	AA	19921018	CA 1991-2085469	19910417
WO 9218626	A1	19921029	WO 1991-FR318	19910417
W: AU, CA, HU, JP, KR, SU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9177927	A1	19921117	AU 1991-77927	19910417
AU 653937	B2	19941020		
EP 537166	A1	19930421	EP 1991-909065	19910417
EP 537166	B1	19990707		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05507614	T2	19931104	JP 1991-508749	19910417
HU 215587	B	19990128	HU 1992-3955	19910417
AT 181961	E	19990715	AT 1991-909065	19910417
ES 2133285	T3	19990916	ES 1991-909065	19910417
PRIORITY APPLN. INFO.:			FR 1990-1298	19900205
			EP 1991-909065	19910417
			WO 1991-FR318	19910417

AB Sol. derivs. of the interferon .alpha. receptor are produced by recombinant animal and prokaryotic cells. CDNA for receptors lacking the transmembrane and cytoplasmic domains were expressed in CHO cells, and CDNA for Ig light or heavy chain fused to this sol. receptor were expressed in Escherichia coli.

L97 ANSWER 11 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE
 5

ACCESSION NUMBER: 1992:300034 BIOSIS
 DOCUMENT NUMBER: BA94:13184
 TITLE: CONVERSION OF HUMAN INTERFERON-BETA
 FROM A SECRETED TO A PHOSPHATIDYLINOSITOL ANCHORED PROTEIN
 BY FUSION OF A 17 AMINO ACID SEQUENCE TO ITS
 CARBOXYL TERMINUS.
 AUTHOR(S): SANTILLAN G E; SANDOVAL M J; CHERNAJOVSKY Y; ORCHANSKY P L
 CORPORATE SOURCE: INSTITUTO INVESTIGACIONES BIOQUIMICAS BAHIA BLANCA INIBIBB,
 C.C. 857, BAHIA BLANCA 8000, ARGENTINA.
 SOURCE: MOL CELL BIOCHEM, (1992) 110 (2), 181-191.
 CODEN: MCBIB8. ISSN: 0300-8177.

FILE SEGMENT: BA; OLD
 LANGUAGE: English

AB A number of cell-surface proteins are anchored in plasma membranes by a glycosylated phosphatidylinositol (PI) moiety that is covalently attached to the carboxyl-terminal amino acid of the mature protein. We have previously reported the construction of a cDNA clone of a truncated Platelet-derived growth factor (PDGF) receptor that consists of the extracellular domain without the transmembrane and cytoplasmic domains. In the construction of the vector, a sequence of 51 base pairs (bp) from the 3'-untranslated region of the receptor cDNA was linked in frame with the external domain coding sequence. The truncated receptor protein with the peptide VTSGHCHEERVDRHDGE fused to its carboxyl terminus was covalently

attached to the membrane by a PI linkage and it was released by phosphatidylinositol specific-phospholipase C (PI-PLC). When the 51 bp sequence was deleted, the external domain receptor protein was secreted into the media. To determine whether the PI linkage of the protein was due to the 17 amino acids added, the peptide was fused to the carboxyl terminus of the secreted protein human **Interferon-.beta.**

(hu-**IFN-.beta.**). Chinese hamster ovary (CHO) cells transfected with the hu-**IFN-.beta.** cDNA secreted the protein to the conditioned media, whereas CHO cells transfected with the carboxyl terminus modified-hu-**IFN-.beta.** cDNA did not secrete detectable levels of protein. CHO cell expressing the carboxyl terminus modified-hu-**IFN-.beta.** were treated with PI-PLC, the media and cell lysates were analyzed by SDS-PAGE after immunoprecipitation with antibodies against hu-**IFN-.beta.**

The modified protein is anchored to the plasma membrane by a PI linkage and it is specifically released by PI-PLC, whereas a control preparation of CHO cells expressing wild type hu-**IFN-.beta.** does not show the same pattern. The 17 amino acid peptide fused to the carboxyl terminus of **IFN-.beta.** directs attachment of a PI anchor and targets the fusion protein to the plasma membrane.

L97 ANSWER 12 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE
6

ACCESSION NUMBER: 1988:331563 BIOSIS
DOCUMENT NUMBER: BA86:38114

TITLE: SYNTHESIS AND SECRETION OF MULTIPLE FORMS OF **BETA**-2 **INTERFERON-B-CELL DIFFERENTIATION FACTOR**
2-HEPATOCYTE-STIMULATING FACTOR BY HUMAN FIBROBLASTS AND MONOCYTES.

AUTHOR(S): MAY L T; GHRAYEB J; SANTHANAM U; TATTER S B; STHOEGER Z;
HELFGOTT D C; CHIORAZZI N; GRIENINGER G; SEHGAL P B

CORPORATE SOURCE: ROCKEFELLER UNIV., 1230 YORK AVE., NEW YORK, N.Y. 10021.

SOURCE: J BIOL CHEM, (1988) 263 (16), 7760-7766.
CODEN: JBCHA3. ISSN: 0021-9258.

FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The cDNA for human **.beta.2-interferon (IFN-.beta.2)**/B-cell differentiation factor 2/hepatocyte-stimulating factor was expressed in Escherichia coli to yield a **fusion** protein which contains the 182 carboxyl-terminal amino acids of **IFN-.beta.2** fused to a 34-amino acid prokaryotic leader peptide (**rIFN-.beta.2**). When added to cultures of human hepatoma cell line Hep3B2, **rIFN-.beta.2** as well as preparations of natural **IFN-.beta.2** enhanced secretion of positive acute phase reactants such as **.alpha.1-antichymotrypsin**, complement C3, fibrinogen, and **.alpha.1-acid glycoprotein** and inhibit secretion of albumin, confirming that a protein derived from the **IFN-.beta.2** gene can have hepatocyte-stimulating factor activity. We have prepared a rabbit polyclonal antiserum to the E. coli-derived human **IFN-.beta.2** fusion protein. This polyclonal antiserum inhibits the hepatocyte-stimulating and B-cell differentiation activities of appropriate **IFN-.beta.2** preparations. The anti-**rIFN-.beta.2** antiserum has been used in immunoprecipitation experiments and in Western blots to help define the secretory proteins derived from the **IFN-.beta.2** gene in fibroblasts and monocytes. "Uninduced" human FS-4 fibroblasts as well as those induced with interleukin-1.**.alpha.**, tumor necrosis factor, or bacterial lipopolysaccharide secrete at least five forms of **IFN-.beta.2** of apparent molecular mass in the range from 23 to 30 kDa which can be resolved by polyacrylamide gel electrophoresis under denaturing and reducing conditions. The three higher molecular mass forms are not observed when FS-4 cells are induced in the presence of tunicamycin, suggesting that these forms are **N-glycosylated**.

(gp28, gp29, and gp30). Although secretion of the two lower molecular mass forms is resistant to tunicamycin, they are labeled by [³H]glucosamine (gp23-gp25). The inclusion of cycloheximide during the [³⁵S)methionine labeling of induced FS-4 cells results in the preferential synthesis and secretion of the 29-kDa triplet. Human monocytes induced with bacterial lipopolysaccharide also secrete several distinct forms of IFN-.
beta.2 in the size range from 23 to 30 kDa which co-migrate in polyacrylamide gels with those obtained from FS-4 cells. Our observations help relate previous description of multiple forms of hepatocyte-stimulating factor to specific proteins derived from the IFN-.
beta.2 gene.

L97 ANSWER 13 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:329330 BIOSIS
DOCUMENT NUMBER: PREV200200329330
TITLE: Biologic therapy of inflammatory bowel disease.
AUTHOR(S): Sandborn, William J. (1); Targan, Stephan R.
CORPORATE SOURCE: (1) Mayo Clinic, 200 First Street SW, Rochester, MN, 55905:
sandborn.william@mayo.edu USA
SOURCE: Gastroenterology, (May, 2002) Vol. 122, No. 6, pp.
1592-1608. <http://www.gastrojournal.org/>. print.
ISSN: 0016-5085.

DOCUMENT TYPE: General Review

LANGUAGE: English

AB Advancing knowledge regarding the biology of chronic inflammation has led to the development of specific biologic therapies that mechanistically target individual inflammatory pathways. Many biologic therapies are being evaluated for the treatment of the chronic inflammatory bowel diseases, Crohn's disease and ulcerative colitis. Biologic compounds proven to be effective for Crohn's disease include monoclonal antibodies to tumor necrosis factor (infliximab and CDP571) and to the leukocyte adhesion molecule alpha4 integrin (natalizumab). Other biologic compounds for which there is insufficient evidence to judge efficacy for inflammatory bowel disease include: p55 tumor necrosis factor binding protein (onercept); **interferon alpha**; **interferon beta-1a**; anti-**interferon gamma** antibody; anti-interleukin 12 antibody; p65 anti-sense oligonucleotide (blocks NF-kappaB); granulocyte colony stimulating factor, and granulocyte macrophage colony stimulating factor; anti-interleukin 2 receptor antibody; epidermal growth factor; keratinocyte growth factor 2 (repifermin); human growth hormone; anti-CD4 antibody; and anti-alpha4beta7 antibody. Biologic therapies that have been proven ineffective for inflammatory bowel disease include: interleukin 10; interleukin 11; anti-sense intercellular adhesion molecule-1; and the tumor necrosis factor receptor **fusion** protein etanercept. Based on the early successes of infliximab, CDP571 and natalizumab, it seems certain that biologic therapy will play an important role in the future treatment of inflammatory bowel disease.

L97 ANSWER 14 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:190854 BIOSIS
DOCUMENT NUMBER: PREV200000190854
TITLE: Systematic mutational mapping of sites on human **interferon-beta-1a** that are important for receptor binding and functional activity.
AUTHOR(S): Runkel, Laura; deDios, Carole; Karpusas, Michael; Betzenhauser, Matthew; Muldowney, Celine; Zafari, Mohammad; Benjamin, Christopher D.; Miller, Stephan; Hochman, Paula S.; Whitty, Adrian (1)
CORPORATE SOURCE: (1) Biogen, Inc., 14 Cambridge Center, Cambridge, MA, 02142 USA
SOURCE: Biochemistry, (March 14, 2000) Vol. 39, No. 10, pp. 2538-2551.
ISSN: 0006-2960.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A systematic mutational analysis of human **interferon-beta-1a** (**IFN-beta**) was performed to identify regions on the surface of the molecule that are important for receptor binding and for functional activity. The crystal structure of **IFN-beta-1a** was used to design a panel of 15 mutant proteins, in each of which a contiguous group of 2-8 surface residues was mutated, in most instances to alanine. The mutants were analyzed for activity in vitro in antiviral and in antiproliferation assays, and for their ability to bind to the type I IFN (ifnar1/ifnar2) receptor on Daudi cells and to a soluble ifnar2 fusion protein (ifnar2-Fc). Abolition of binding to ifnar2-Fc for mutants A2, AB1, AB2, and E established that the ifnar2 binding site on IFN-beta comprises parts of the A helix, the AB loop, and the E helix. Mutations in these areas, which together define a contiguous patch of the IFN-beta surface, also resulted in reduced affinity for binding to the receptor on cells and in reductions in activity of 5-50-fold in functional assays. A second receptor interaction site, concluded to be the ifnar1 binding site, was identified on the opposite face of the molecule. Mutations in this region, which encompasses parts of the B, C, and D helices and the DE loop, resulted in disparate effects on receptor binding and on functional activity. Analysis of antiproliferation activity as a function of the level of receptor occupancy allowed mutational effects on receptor activation to be distinguished from effects on receptor binding. The results suggest that the binding energy from interaction of IFN-beta with ifnar2 serves mainly to stabilize the bound IFN/receptor complex, whereas the binding energy generated by interaction of certain regions of IFN-beta with ifnar1 is not fully expressed in the observed affinity of binding but instead serves to selectively stabilize activated states of the receptor.

L97 ANSWER 15 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:71065 BIOSIS
DOCUMENT NUMBER: PREV200000071065
TITLE: IFN-tau inhibits IgE production in a murine model of allergy and in an IgE-producing human myeloma cell line.
AUTHOR(S): Mujtaba, Mustafa G. (1); Villarete, Lorelie; Johnson, Howard M.
CORPORATE SOURCE: (1) Department of Microbiology and Cell Science, University of Florida, Bldg 981, Room 1052, Gainesville, FL USA
SOURCE: Journal of Allergy and Clinical Immunology, (Nov., 1999)
Vol. 104, No. 5, pp. 1037-1044.
ISSN: 0091-6749.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: IFN-tau, a type I IFN, is an antiviral, immunomodulating, and antiproliferative agent similar to **IFN-alpha** and **IFN-beta**, but IFN-tau lacks the toxicity associated with high concentrations of these IFNs in tissue culture and in animal studies. We have previously shown that IFN-tau inhibits antibody production in a murine model of an autoimmune disease. Objective: We investigate the effectiveness of ovine IFN-tau and other type I IFNs in suppressing the development of allergic sensitization in a murine model of allergy by using ovalbumin (OVA) antigen as an allergen and in suppressing IgE production by using a human IgE-producing myeloma cell line. Methods and Results: Mice that were treated with IFN-tau in vivo before and after intraperitoneal immunization with aluminum hydroxide-precipitated OVA had significantly lower OVA-specific IgE levels than the PBS-treated group. IFN-tau-treated mice had reduced inflammatory cell infiltration into the lung tissue. Furthermore, in vitro IFN-tau treatment of splenocytes taken from OVA-immunized mice

suppressed OVA-induced proliferation. Also, treatment of the IgE-producing human myeloma cell line U266BL with IFN-tau-reduced IgE production and inhibited cell proliferation compared with media controls. Similar suppression of proliferation and inhibition of IgE production was seen with other type I IFNs, as well as a humanized IFN-tau/IFN-alphaD **chimeric** that consists of residues 1 to 27 of the ovine IFN-tau and residues 28 to 166 of the human IFN-alphaD. The **chimeric** was not toxic to human peripheral white blood cells at concentrations as high as 105 U/mL, whereas human IFN-alphaD was toxic at 103 U/mL. Conclusion: These data suggest that IFNs may be useful in preventing allergic sensitization by suppressing the production of allergen-specific IgE antibodies without toxic side effects.

L97 ANSWER 16 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:349124 BIOSIS

DOCUMENT NUMBER: PREV199800349124

TITLE: The evolution of B precursor leukemia in the Emu-ret mouse.

AUTHOR(S): Wasserman, Robert (1); Zeng, Xiang-Xing; Hardy, Richard R.

CORPORATE SOURCE: (1) Div. Oncol., Child. Hosp. Phila., 34th and Civic Center Blvd., Philadelphia, PA 19104 USA

SOURCE: Blood, (July 1, 1998) Vol. 92, No. 1, pp. 273-282.

ISSN: 0006-4971.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Emu-ret mice carrying an RFP/RET fusion gene under the transcriptional control of the immunoglobulin heavy chain enhancer develop B lineage leukemias/lymphomas. We have characterized B-cell development in these mice before the onset of clinical disease to determine the steps involved in leukemogenesis. Flow cytometry reveals that the CD45R+CD43+CD24+BP-1+ late pro-B-cell population is markedly expanded in the bone marrow of 3- to 5-week-old Emu-ret mice. Compared with late pro-B cells from transgenenegative mice, Emu-ret late pro-B cells have a limited capacity to differentiate in interleukin (IL)-7 and a higher incidence of VDJ rearrangements, but a similar cell cycle profile. In contrast, CD45R+CD43+CD24+BP-1 - early pro-B cells from 3- to 5-week-old Emu-ret mice, which also express the RFP/RET transgene, differentiate in IL-7 similarly to their normal counterparts. Furthermore, early pro-B cells from Emu-ret and transgene-negative mice have an identical pattern of growth inhibition when exposed to **interferons** (IFNs)-alpha/beta and -gamma, whereas, pro-B-cell leukemia lines derived from Emu-ret mice are markedly less sensitive to growth inhibition by these IFNs. In 13-week-old well-appearing Emu-ret mice, late pro-B cells upregulate CYCLIN D1 expression and downregulate CASPASE-1 expression in a pattern that correlates with the emergence of B precursor cells in the peripheral blood and the loss of other B lineage subsets in the bone marrow. Taken together, these results suggest that the expression of the RFP/RET transgene initially prevents the normal elimination of late pro-B cells with nonproductive rearrangements. Secondary events that simultaneously disturb the normal transcriptional regulation of genes involved in the control of the cell cycle and apoptosis may allow for subsequent malignant transformation within the expanded late pro-B-cell population.

L97 ANSWER 17 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:116068 BIOSIS

DOCUMENT NUMBER: PREV199800116068

TITLE: Bovine type I interferon receptor protein BoIFNAR-1 has high-affinity and broad specificity for human type I interferons.

AUTHOR(S): Langer, Jerome A. (1); Yang, Jianliang; Carmillo, Paul; Ling, Leona E.

CORPORATE SOURCE: (1) Dep. Mol. Genet. Microbiol., Robert Wood Johnson Med. Sch.-UMDNJ, Piscataway, NJ 08854 USA

SOURCE: FEBS Letters, (Jan. 9, 1998) Vol. 421, No. 2, pp. 131-135.
ISSN: 0014-5793.

DOCUMENT TYPE: Article
LANGUAGE: English

AB The type I interferon receptor (IFNAR1) is composed of two transmembrane polypeptides, IFNAR-1 and IFNAR-2. Human IFNAR-1 has low intrinsic affinity for IFNs, but enhances the affinity for IFNs of the complex over that of HuIFNAR-2 alone, and modulates the ligand specificity. Bovine cells respond to human alpha interferons. The bovine homologue of HuIFNAR-1, BoIFNAR-1, when expressed in heterologous cells, confers high-affinity binding and broad specificity for human type I IFNs. A soluble **fusion** protein of the ectodomain of BoIFNAR-1 and an **immunoglobulin** Fc domain was produced. In contrast to HuIFNAR-1, this protein competes strongly with human cells for IFN binding, and directly binds a wide spectrum of human type I IFNs, including diverse **IFN-alpha**s, **IFN-beta** and **IFN-omega**, with moderate to high affinity. This accounts for much of the specificity for human IFNs possessed by bovine cells, with several exceptions. The BoIFNAR-1 ectodomain, in contrast to HuIFNAR-1, may be useful for studies of binary and ternary complexes with IFNs and IFNAR-2, and for purification, assay and biological neutralization protocols.

L97 ANSWER 18 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1994:546391 BIOSIS

DOCUMENT NUMBER: PREV199598005939

TITLE: Characterization of a CD6 ligand(s) expressed on human- and murine-derived cell lines and murine lymphoid tissues.

AUTHOR(S): Wee, Siow-Fong (1); Wang, Wei-Chun; Farr, Andrew G.; Nelson, Andrew J.; Patel, Dhavalkumar D.; Haynes, Barton F.; Linsley, Peter S.; Aruffo, Alejandro

CORPORATE SOURCE: (1) Immunex Corp., Seattle, WA 98101 USA

SOURCE: Cellular Immunology, (1994) Vol. 158, No. 2, pp. 353-364.
ISSN: 0008-8749.

DOCUMENT TYPE: Article
LANGUAGE: English

AB CD6, a type I cell surface glycoprotein expressed predominantly by thymocytes and mature T lymphocytes, becomes phosphorylated on tyrosine residues following T cell activation and has been implicated as an accessory molecule in T cell activation. The purpose of this study was to identify cell lines and tissues which express CD6 ligand(s), determine the requirements for CD6 binding, and biochemically characterize the putative CD6 ligand(s). Binding studies with a CD6 **immunoglobulin** **fusion** protein, CD6-Rg, allowed the identification of a number of human cell lines which express a CD6 ligand(s). The binding to these cell lines was trypsin sensitive, in part required divalent cations, was blocked by an anti-CD6 mAb, and could be downregulated by tumor necrosis factor alpha (TNF-alpha), interleukin-1-beta (IL-1-**beta**) and **interferon-gamma** (**IFN-gamma**). Among the cell lines tested, the human breast carcinoma-derived cell line HBL-100 expressed the highest levels of CD6 ligand(s) and was used for immunoprecipitation studies. Following metabolic labeling, CD6-Rg immunoprecipitated glycoproteins of apprx 100, apprx 90, and apprx 45 kDa from HBL-100 cells. Using CD6-Rg we were able to show that murine thymus, lymph nodes, and skin express high levels of CD6 ligand(s) and that CD6-Rg bound to a murine thymic epithelial cell line and to cultured human epidermal keratinocytes.

L97 ANSWER 19 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1991:340961 BIOSIS

DOCUMENT NUMBER: BA92:40336

TITLE: A PROTEIN WITH A BINDING SPECIFICITY SIMILAR TO NF-KAPPA-B BINDS TO A STEROID-DEPENDENT REGULATORY ELEMENT IN THE OVALBUMIN GENE.

AUTHOR(S): SCHWEERS L A; SANDERS M M
CORPORATE SOURCE: DEP. BIOCHEMISTRY, UNIVERSITY MINNESOTA, MINNEAPOLIS, MINN.
55455.
SOURCE: J BIOL CHEM, (1991) 266 (16), 10490-10497.
CODEN: JBCHA3. ISSN: 0021-9258.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The chicken ovalbumin gene is regulated at the level of transcription by four classes of steroid hormones. A steroid-dependent regulatory element (SDRE) found from -900 to -732 is required for this steroid-mediated induction. To define more precisely sequences of the SDRE required for steroid induction, a series of exonuclease III deletions were made in the 3' end of the SDRE. **Fusion** genes containing the mutant ovalbumin 5'-flanking sequences linked to the chloramphenicol acetyltransferase structural gene (CAT) were transfected into steroid-responsive primary oviduct cells. These functional studies defined a region of the SDRE from -793 to -759 that is essential for induction by steroids. Analysis of protein interactions in this 34-base pair region by copper-phenanthroline footprinting and methylation interference assays defined nucleotides required for protein binding. Footprinting showed protection of residues extending from -784 to -765, an area that included nucleotides that, when methylated, interfered with protein binding. In addition, this footprinted region contained 10 nucleotides that were identical to sequences contained in the **.beta.-interferon** gene regulatory element. An oligomer synthesized to this region of homology produced two DNA-protein complexes with oviduct nuclear proteins. Although this region of the interferon gene regulatory element binds the transcription factor NF-.kappa.B, an oligomer from the immunoglobulin .kappa. light chain gene known to bind NF-.kappa.B did not compete with the SDRE oligomer for binding to oviduct nuclear proteins. Surprisingly, this same NF-.kappa.B oligomer was able to restore steroid responsiveness to an SDRE mutant, while an oligomer from the immunoglobulin heavy chain gene inserted in the same position did not affect induction by steroids. These data suggest that a protein binding to sequences in the SDRE that are similar to an NF-.kappa.B-binding site participates in the steroid-mediated increase in transcription of the chicken ovalbumin gene.

L97 ANSWER 20 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:124937 BIOSIS
DOCUMENT NUMBER: BA87:59590
TITLE: HIGH-LEVEL EXPRESSION OF A BIOENGINEERED CYSTEINE-FREE HEPATOCYTE-STIMULATING FACTOR INTERLEUKIN 6-LIKE PROTEIN.
AUTHOR(S): JAMBOU R C; SNOOWAERT J N; BISHOP G A; STEBBINS J R; FRELINGER J A; FOWLKES D M
CORPORATE SOURCE: DEP. PATHOL., UNIV. NORTH CAROLINA, CHAPEL HILL, NC 27599.
SOURCE: PROC NATL ACAD SCI U S A, (1988) 85 (24), 9426-9430.
CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Hepatocyte-stimulating factor, **interferon-.beta.2**, B-cell stimulation factor 2, and hybridoma/plasmacytoma growth factor are identical proteins presently referred to as interleukin 6 (IL-6). Through the use of synthetic oligonucleotide technology, we have constructed a biologically active recombinant IL-6 (rIL-6) gene based on the sequence of a human IL-6 cDNA. The synthetic gene encodes a cysteine-free, bioengineered rIL-6 protein that is expressed at high levels in *Escherichia coli* as a tripartite **fusion** protein. Cleavage of the **fusion** protein with collagenase releases a 23-kDa rIL-6 protein that can be easily purified to homogeneity. We show that the rIL-6 protein displays a range of biological activities similar to those of natural human IL-6, as demonstrated by its ability to (i) protect cells from viral infection, (ii) stimulate the synthesis of fibrinogen in rat

FAZA 967 cells, and (iii) induce the terminal differentiation of B cells, resulting in elevated secretion of **immunoglobulin**.

L97 ANSWER 21 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1987:312636 BIOSIS

DOCUMENT NUMBER: BA84:32143

TITLE: B CELL GROWTH MODULATING AND DIFFERENTIATING ACTIVITY OF RECOMBINANT HUMAN 26-KD PROTEIN BSF-2 HUIFN-BETA-2 HPGF.

AUTHOR(S): POUPART P; VANDENABEELE P; CAYPHAS S; VAN SNICK J; HAEGEMAN G; KRUYS V; FIERS W; CONTENT J

CORPORATE SOURCE: PASTEUR INST. BRABANT, DEP. VIROL., B-1180 BRUSSELS.

SOURCE: EMBO (EUR MOL BIOL ORGAN) J, (1987) 6 (5), 1219-1224.

CODEN: EMJODG. ISSN: 0261-4189.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The human '26-kd protein' is secreted glycoprotein expressed, for example, in (blood) leukocytes, in epithelial cells treated with various inducers, but most strongly in interleukin-1 (IL-1)-treated fibroblasts. After finding it had antiviral and 2'-5A synthetase-inducing activity, one group of authors called this protein **IFN-.beta.2**. However, recently the full-length 26-kd cDNA sequence was shown to be identical with that of a B-cell-differentiating lymphokine called BSF-2, and another report suggested that the 26-kd protein could support the growth of some transformed murine B cell lines. To define its biological activities, we expressed the recombinant 26-kd protein by translating to *Xenopus laevis* oocytes a pure, synthetic **chimeric** mRNA containing the 26-kd protein coding region surrounded by *Xenopus laevis* .beta.-globin untranslated regions. A similar construction, but containing the HuIFN-.beta. cDNA coding region, was used to produce HuIFN-.beta. by the same procedure. Both recombinant glycoproteins were secreted, **glycosylated**, and their amounts were measured by [35S]methionine incorporation by the oocyte. Here we show that the recombinant 26-kd protein exhibits a high growth factor activity when assayed on an IL-HP1-dependent murine B cell hybridoma (sp. act. .apprx. 2 .times. 108 U/mg) as well as a potent differentiating activity on human CESS cells (sp. act .apprx. 5 .times. 107 U/mg) While rHuIFN-.beta. was inactive in the latter two assays, it had the expected antiviral activity of 1-5 .times. 108 U/mg. The parallel recombinant 26-kd protein preparations had no detectable antiviral activity (i.e. a maximal specific activity of 1-3 .times. 102 U/mg, if any). The 26-kd protein is thus clearly an interleukin, and considering the confusing nomenclature now in use, this factor may better be renamed 'interleukin 6'.

L97 ANSWER 22 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1983:214651 BIOSIS

DOCUMENT NUMBER: BA75:64651

TITLE: THE HUMAN FIBROBLAST AND HUMAN IMMUNE INTERFERON GENES AND THEIR EXPRESSION IN HOMOLOGOUS AND HETEROLOGOUS CELLS.

AUTHOR(S): FIERS W; REMAUT E; DEVOS R; CHEROUTRE H; CONTRRAS R; GHEYSEN D; DEGRAVE W; STANSSENS P; JAVERNIER J; TAYA Y; CONTENT J

CORPORATE SOURCE: LAB. MOLECULAR BIOL., STATE UNIV. GHENT, LEDEGANCKSTR. 35, B-9000 GHENT, BELGIUM.

SOURCE: PHILOS TRANS R SOC LOND B BIOL SCI, (1982) 299 (1094), 29-38.

CODEN: PTRBAE. ISSN: 0080-4622.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The genetic information coding for human fibroblast **interferon** (**IFN-.beta.**) was cloned both as a DNA copy (cDNA) and as a genomic clone. Human **IFN-.beta.** is made as a precursor and consists of a signal sequence 21 amino acid residues long followed by the mature protein 166 amino acids long. A single site for

glycosylation is present. The human IFN-.beta. gene does not contain introns. Transfection of monkey cells with a chimeric SV40 derivative containing the human IFN-.beta. cDNA clone under control of the late SV40 promoter leads to secretion of high levels of IFN-.beta.. When a genomic clone is used in the same vector, IFN-.beta. synthesis can be further enhanced up to 30-fold by treatment with poly(rI).cntdot.poly(rC); this shows that a cis-active control element is present in the clone. An efficient expression system in Escherichia coli was worked out based on a plasmid containing the promoter of PL of bacteriophage .lambda., which is regulated by a temperature-sensitive repressor. This promoter is followed by a segment derived from bacteriophage MS2 that contains the ribosome-binding site of the replicase gene. The latter, however, is replaced by the human IFN-.beta. gene. Upon induction, high levels (about 5 .apprx. 10⁹ IU l-1) of IFN-.beta. are synthesized by the bacteria; this corresponds to about 2% of the total bacterial protein. The human immune (type II) interferon (IFN-.gamma.) gene was similarly cloned. Partly purified mRNA derived from human spleen cells that had been induced with staphylococcal enterotoxin A was used as starting material. A full-length cDNA clone was sequenced. The total cDNA sequence is about 1150 nucleotides long; it contains a single open reading frame coding for 166 amino acids, the first 20 of which constitute the transmembrane signal. There are 2 sites for glycosylation. The amino acid sequence is quite different from that of IFN-.alpha. or IFN-.beta., although a few similarities can be noted. The untranslated 3'-terminal region is about 550 nucleotides long. The IFN-.gamma. gene was expressed in monkey cells, again by using the SV40-derived vector, and the secreted product was characterized as true human IFN-.gamma.. A genomic clone in the form of a bacteriophage .lambda. derivative was also obtained. The IFN-.gamma. gene extends over at least 5 kilobases and contains at least 2 introns.

L97 ANSWER 23 OF 38 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V. DUPLICATE
ACCESSION NUMBER: 1998:28077754 BIOTECHNO

TITLE: Cloning and expression of murine IFN.beta. and a TNF antagonist for gene therapy of experimental allergic encephalomyelitis

AUTHOR: Triantaphyllopoulos K.A.; Croxford J.L.; Baker D.; Chernajovsky Y.

CORPORATE SOURCE: Y. Chernajovsky, Kennedy Institute of Rheumatology, 1 Aspenlea Road, Hammersmith, London W6 8LH, United Kingdom.

SOURCE: Gene Therapy, (1998), 5/2 (253-263), 44 reference(s)
CODEN: GETHEC ISSN: 0969-7128

DOCUMENT TYPE: Journal; Article

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Immunomodulation of an ongoing autoimmune disease can be achieved by inhibitory cytokines or cytokine inhibition such as TNF antagonists, delivered by gene therapy. The aim of this study was to design and test plasmid and retrovirus vectors expressing the mouse IFN.beta. gene and a chimeric protein containing the extracellular domain of human p55 TNF receptor linked to a murine Ig. These vectors were transiently expressed in COS-7 cells and permanently in amphotropic packaging cell lines or ABH mouse immortalized fibroblasts. Expression levels were assessed by ELISA, Western blotting and biological activity. In order to achieve tissue-specific expression in the CNS, the IFN.beta. gene was cloned and expression under the control of the rat NSE promoter. We evaluated these constructs by direct intracranial injections of DNA-liposome complexes during the induction phase of experimental allergic encephalomyelitis, a murine model of multiple sclerosis, with therapeutic benefit.

L97 ANSWER 24 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002188730 EMBASE
TITLE: Juvenile rheumatoid arthritis: Therapeutic perspectives.
AUTHOR: Chikanza I.C.
CORPORATE SOURCE: Dr. I.C. Chikanza, Bone and Joint Research Unit, St. B./R.
L. School of Med./Dent., Charterhouse Square, London EC1M
6BQ, United Kingdom. i.c.chikanza@qmul.ac.uk
SOURCE: Paediatric Drugs, (2002) 4/5 (335-348).
Refs: 153
ISSN: 1174-5878 CODEN: PTDGFW
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
030 Pharmacology
031 Arthritis and Rheumatism
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Juvenile rheumatoid arthritis (JRA) is the most common childhood chronic systemic autoimmune inflammatory disease. The therapeutic approach to JRA has, to date, been casual and based on extensions of clinical experiences gained in the management of adult rheumatoid arthritis (RA). The physiology of inflammation has been systemically studied and this has led to the identification of specific therapeutic targets and the development of novel approaches to the management of JRA. The classical treatments of the disease such as methotrexate, sodium aurothiomalate and sulfasalazine, are not always effective in controlling RA and JRA. This has necessitated the development of novel agents for treating RA, most of which are biological in nature and are targeted at specific sites of the inflammatory cascades. These biological therapeutic strategies in RA have proved successful and are being applied in the management of JRA. These developments have been facilitated by the advances in molecular biology which have heralded the advent of biologics (recombinant proteins) and gene therapy, in which specific genes can be introduced locally to enhance in vivo gene expression or suppress gene(s) of interest with a view to down-regulating inflammation. Some of these biologics, such as anti-tumor necrosis factor .alpha. (anti-TNF.alpha.), monoclonal antibodies (infliximab, adalimumab), TNF soluble receptor constructs (etanercept) and interleukin-1 receptor antagonist (IL-1Ra) have been tested and shown to be effective in RA. Etanercept has now been licensed for JRA. Clinical trials of infliximab in JRA are planned. Studies show that the clinical effects are transient, necessitating repeated treatments and the risk of vaccination effects. Anti-inflammatory cytokines such as IL-4, IL-10, transforming growth factor-.beta. and interferon-.beta. (IFN-.beta.) are undergoing clinical trials. Many of these agents have to be administered parenterally and production costs are very high; thus, there is a need, especially for pediatric use, to develop agents that can be taken orally. Long-term studies will be required to assess the tolerability and toxicity of these approaches in JRA, since cytokines and other mediators play important roles in host defenses, and the chronic inhibition, exogenous administration or constitutive over-expression of some cytokines/mediators may have undesirable effects.

L97 ANSWER 25 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001289286 EMBASE
TITLE: Measurement of antibodies to interferon beta in patients with multiple sclerosis.
AUTHOR: Pachner A.R.
CORPORATE SOURCE: Dr. A.R. Pachner, Department of Neurosciences, University of Medicine and Dentistry, New Jersey Medical School, 185

SOURCE: Orange Ave, Newark, NJ 07103, United States
Archives of Neurology, (2001) 58/8 (1299-1300).
Refs: 14
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L97 ANSWER 26 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002050229 EMBASE
TITLE: Induction of tolerance to recombinant therapeutic proteins.
AUTHOR: Meritet J.-F.; Maury C.; Tovey M.G.
CORPORATE SOURCE: Dr. M.G. Tovey, Laboratory of Viral Oncology, CNRS-UPR
9045, 7, rue Guy Moquet, 94801 Villejuif, France.
tovey@vjf.cnrs.fr
SOURCE: Journal of Interferon and Cytokine Research, (2001) 21/12
(1031-1038).
Refs: 17
ISSN: 1079-9907 CODEN: JICRFJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The specific IgM and IgG antibody responses to subcutaneous (s.c.) treatment of mice with recombinant human IFN-.alpha.2a (rHuIFN-.alpha.2a) or IFN-.beta. were inhibited in a dose-dependent manner by prior oromucosal (o.m.) administration of rHuIFN-.alpha.2a or IFN-.beta., respectively. Pretreatment of animals once a day for 7 days by the o.m. route with the highest dose of IFN-.alpha.2a tested (10(7) IU) resulted in complete inhibition of the peak IFN-.alpha.2a-specific IgG antibody response detected 28 days after subsequent s.c. injection of IFN-.alpha.2a ($p < 0.001$). Similarly, prior o.m. administration of 1-10 .mu.g rHuGM-CSF per day for 7 days resulted in a statistically significant ($p < 0.001$) inhibition of the peak GM-CSF-specific IgG antibody response detected 28 days after s.c. administration of GM-CSF. In contrast, prior o.m. treatment with a quantity of bovine serum albumin (BSA) (100 .mu.g) or human serum albumin (HSA) (10 .mu.g) equivalent, respectively, to the protein content of the highest dose of IFN-.alpha.2a or GM-CSF administered by the o.m. route, did not affect significantly the IFN-.alpha.2a-specific or GM-CSF-specific IgG antibody responses detected on subsequent s.c. administration of IFN-.alpha.2a or GM-CSF. Oromucosal administration of IFN-.alpha.2a, IFN-.beta., or GM-CSF alone did not induce detectable IFN-.alpha.2a-specific, IFN-.beta.-specific, or GM-CSF-specific IgM or IgG antibody responses at any of the time points tested. These results suggest that short-term o.m. administration of a recombinant protein is an effective means of inducing peripheral tolerance to subsequent parenteral administration of a therapeutic protein.

L97 ANSWER 27 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001012624 EMBASE
TITLE: Biopharmaceuticals approved in the EU 1995-1999: A European Union-United States comparison.
AUTHOR: Reichert J.M.; Healy E.M.
CORPORATE SOURCE: J.M. Reichert, Tufts Center, Study of Drug Development, 192 South Street, Boston, MA 02111, United States.
janice.reichert@tufts.edu
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics,

(2001) 51/1 (1-7).
Refs: 13
ISSN: 0939-6411 CODEN: EJPBEL
PUBLISHER IDENT.: S 0939-6411(00)00131-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The European Union's (EU) centralized procedure for new drug review was implemented in 1995 to unify the regulatory process and provide EU-wide marketing authorizations for innovative medicinal products. Goals were instituted to ensure the timeliness of the various steps of the process. The EU approved 27 biopharmaceutical products through the centralized procedure during 1995-1999. This study documents the success of the EU in meeting the timeline goals for the group and for separate categories of biopharmaceuticals (recombinant proteins, monoclonal antibodies, and antisense oligonucleotides). A subset of the 27 biopharmaceuticals approved in the EU were also approved in the United States (US). We compared EU and US approval times for these products by product category and by review status (exceptional/non-exceptional circumstance in the EU and priority/standard in the US). Copyright .COPYRGT. 2001 Elsevier Science B.V.

L97 ANSWER 28 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999206181 EMBASE
TITLE: [Genetically produced drugs: From authentic proteins to muteins and chimeras].
GENTECHNISCH HERGESTELLTE ARZNEIMITTEL: VON AUTHENTISCHEN PROTEINEN ZU MUTEINEN UND CHIMAREN.
AUTHOR: Zundorf I.
CORPORATE SOURCE: Dr. I. Zundorf, Institut Pharmazeutische Biologie, Marie-Curie-Strasse 9, 60439 Frankfurt, Germany.
zuendorf@em.uni-frankfurt.de
SOURCE: Pharmazeutische Zeitung, (3 Jun 1999) 144/22 (11-17).
Refs: 18
ISSN: 0031-7136 CODEN: PZSED5
COUNTRY: Germany
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 022 Human Genetics
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: German

L97 ANSWER 29 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999385486 EMBASE
TITLE: [A growing market].
UN MARCHE A LA DYNAMIQUE COMPLEXE.
AUTHOR: Deroin P.
SOURCE: Biofutur, (1998) -/184 (74-78).
ISSN: 0294-3506 CODEN: BIOFEM
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: French

L97 ANSWER 30 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97317261 EMBASE
DOCUMENT NUMBER: 1997317261
TITLE: [Cytokines - Analytical procedures and their diagnostic

use].
CYTOKINY - ANALYTICKE POSTUPY A INDIKACE VYSETRENI.

AUTHOR: Masek Z.
CORPORATE SOURCE: Dr. Z. Masek, Oddeleni Klinicke Biochemie, Vseobecna Fakultni Nemocnice, I Lekarska Fakulta, Univ. Karlova, Karlovo namesti 32, 121 11 Praha 2, Czech Republic
SOURCE: Klinicka Biochemie a Metabolismus, (1997) 5/SUPPL. (57-59).
ISSN: 1210-7921 CODEN: KBMEFQ
COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: Czech

SUMMARY LANGUAGE: English; Czech

AB Classification of the large group of cytokines is based on various criteria involving results from both basic and clinical research: (1) similarity of in vitro and in vivo physiological and pathophysiological effects (2) type of source and target cells and (3) receptor structure and signal transduction. Analytical procedures evaluating local and/or systemic cytokine levels include different assay approaches, mainly DNA and RNA molecular biology techniques, receptor binding, flow cytometry and broad spectrum of bio- and immunoassays. The choice of the analytical system seems to be the most important factor influencing final results. Indeed, the best (but expensive and time-consuming) method of result validation is to combine different assay groups. International recombinant cytokine standards are now available, but a different degree of antigen glycosylation, fluctuations of the affinity and activity antibody raised, preanalytical factors especially preparation and material storage, matrix effects, presence of soluble cytokine receptors etc. represent serious problems for interlaboratory quality control and results comparison. However, the principal reason for diagnostic use of the cytokine determination in humans has been established: primary and secondary immunohaematology deficiency or proliferation, oncology, infection immunity, and allergic diseases, psoriasis, neurodegenerative disorders and transplantation medicine. Moreover, there is an urgent task for laboratory medicine regarding cytokine levels monitoring in patients receiving cytokine pharmacotherapy (responders and non-responders).

L97 ANSWER 31 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96287027 EMBASE
DOCUMENT NUMBER: 1996287027
TITLE: Methylotrophic yeast Hansenula polymorpha as production organism for recombinant pharmaceuticals.
AUTHOR: Gellissen G.; Melber K.
CORPORATE SOURCE: Rhein Biotech GmbH, Eichsfelder Str. 11,D-40595 Dusseldorf, Germany
SOURCE: Arzneimittel-Forschung/Drug Research, (1996) 46/9 (943-948).
ISSN: 0004-4172 CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
022 Human Genetics
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English; German

AB Since the onset of genetic engineering, yeasts belong to the preferred host cells for the production of heterologous proteins. They combine ease of genetic manipulation and cultivation with the ability to process and to modify the produced compounds according to a general eukaryotic scheme.

Since yeasts do not contain pathogens, pyrogens or viral inclusions they constitute attractive production systems for proteins considered for therapeutic administration. At the beginning of gene technology the attention of biotechnologists focussed on the use of the best characterized species *Saccharomyces cerevisiae*. Insulin and hepatitis B vaccines are examples for *S. cerevisiae*-derived therapeutics. In recent years alternative yeast have become accessible for the techniques of modern molecular genetics and thus for potential applications in biotechnology. In this respect the methylotrophic yeast *Hansenula polymorpha* offers especially advantageous characteristics as host for the production of pharmaceutical proteins. As a consequence, production systems based on this yeast have been established for serum proteins, vaccines and other therapeutically important compounds. Some *H. polymorpha*-derived products are under preclinical or clinical trials at present and are expected to reach the market within the near future. In the following article the current status of this system is presented and discussed comparing it with other expression systems.

L97 ANSWER 32 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2002-154749 [20] WPIDS
 DOC. NO. CPI: C2002-048416
 TITLE: Novel regulatory elements including nucleic acid encoding hybrid alpha-lactalbumin promoter or mutant RNA export element, for expressing one or more proteins e.g. antibodies, pharmaceutical proteins in host cells.
 DERWENT CLASS: B04 D16
 INVENTOR(S): BLECK, G T
 PATENT ASSIGNEE(S): (GALA-N) GALA DESIGN INC
 COUNTRY COUNT: 96
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002002783 A2	20020110 (200220)*	EN	151		
RW:	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW				
AU 2001070252 A	20020114 (200237)				

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002002783 A2		WO 2001-US20714	20010629
AU 2001070252 A		AU 2001-70252	20010629

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001070252 A	Based on	WO 200202783

PRIORITY APPLN. INFO: US 2000-215851P 20000703

AB WO 200202783 A UPAB: 20020402

NOVELTY - A novel regulatory element (I) chosen from a nucleic acid encoding a hybrid bovine/human alpha-lactalbumin (alpha-LA) promoter/enhancer, having a 2101 base pair sequence (S1), fully defined in the specification, encoding a mutant RNA export element (pre-mRNA processing enhancer, PPE), comprising a 244 base pair sequence (S2), fully defined in the specification, or their hybridizable sequences, is new.

DETAILED DESCRIPTION - A novel regulatory element (I) chosen from a nucleic acid encoding a hybrid bovine/human alpha -lactalbumin (alpha -LA) promoter/enhancer, having a 2101 base pair sequence (S1), fully defined in the specification, encoding a mutant RNA export element (pre-mRNA processing enhancer, PPE), comprising a 244 base pair sequence (S2), fully defined in the specification, or their hybridizable sequences, is new. (I) comprises:

- (a) a nucleic acid sequence encoding hybrid bovine/human alpha -LA promoter or its hybridizable sequence, which contains sequences derived from two mammalian sources and causes mammary specific gene expression;
- (b) a nucleic acid sequence encoding mutant RNA export element or its hybridizable sequence which comprises ATG sequences that have been mutated at one of the positions corresponding to nucleic acid residues 4, 112, 131 and 238 of (S2); or
- (c) a nucleic acid sequence encoding a internal ribosome entry site (IRES) coding sequence and a signal peptide coding sequence, which are adjacent to one another.

INDEPENDENT CLAIMS are also included for the following:

- (1) a vector (II) comprising (I);
- (2) a host cell (III) comprising (II); and
- (3) an antibody produced by introducing a vector comprising exogenous genes encoding immunoglobulin genes into a host cell.

USE - (I) and (II) are useful for expression of proteins of interest in a host cell. A vector comprising at least two exogenous genes encoding a protein operably linked to a bovine/human hybrid alpha -LA promoter, where the genes are arranged in a polycistronic sequence separated by an IRES/bovine alpha -LA promoter signal peptide, and a mutant PPE element, is introduced into a host under conditions so that expression of the protein encoded by the exogenous gene is expressed. The regulatory sequences and vector are useful for producing an **immunoglobulin (Ig)**, preferably secretory Ig, where a vector comprising a first and second exogenous genes which encode first and second Ig chain, separated by an IRES is introduced into a host cell under conditions so that the **immunoglobulin** chains are expressed. One of the first and second Ig chains is an Ig light chain such as kappa or lambda light chain, and the other is an Ig heavy chain such as alpha , mu , gamma , delta or epsilon heavy chain. The vector further comprises a bovine alpha -LA signal peptide and bovine/human hybrid alpha -LA promoter. The first and second antibody chains are expressed at a ratio of 0.9:1.1. The vector is a pseudotyped retroviral vector or a plasmid vector. (All claimed). (I) and (II) are useful in the expression of one or more proteins such as erythropoietin, alpha -interferon, alpha -1 proteinase inhibitor, angiogenin, antithrombin III, beta -acid decarboxylase, human growth hormone, bovine growth hormone, porcine growth hormone, human serum albumin, **beta -interferon**, calf intestine alkaline phosphatase, cystic fibrosis transmembrane regulator, factor VIII, factor IX, factor X, insulin, lactoferrin, tissue plasminogen activator, myelin basic protein, insulin, proinsulin, prolactin, hepatitis B antigen, **immunoglobulins**, monoclonal antibody CTLA4 Ig, Tag72 monoclonal antibody, Tag 72 single chain antigen binding protein, protein C, cytokines and their receptors, hormones, von Willebrands factor, lung surfactant, serum albumins, DNase, vascular endothelial growth factor, receptors for hormones or growth factors, rheumatoid factors, nerve growth factors, transforming growth factor, insulin-like growth factor, CD proteins, osteoinductive factors, immunotoxins, bone morphogenetic protein, interferons, colony stimulating factors, interleukins, superoxide dismutase, T-cell receptors, surface membrane proteins, viral antigens, transport proteins, addressins, regulatory proteins, antibodies, **chimeric** proteins, and their fragments. The vectors are particularly useful for expressing G protein coupled receptors and other transmembrane proteins. The retroviral vectors are useful for expressing proteins in mammalian tissue culture host cells, including rat fibroblast

cells, bovine kidney cell and human kidney cells.
Dwg.0/17

L97 ANSWER 33 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2002-122028 [16] WPIDS
 DOC. NO. CPI: C2002-037345
 TITLE: Replication-incompetent recombinant virus useful as vaccine for immunizing humans against pathogenic virus, bacteria and parasites, has antigens heterologous to the virus and an immuno-stimulator sequence.
 DERWENT CLASS: B04 D16
 INVENTOR(S): WANG, D
 PATENT ASSIGNEE(S): (GENP-N) GENPHAR INC
 COUNTRY COUNT: 96
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001091536 A2		20011206 (200216)*	EN	142	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001071288 A		20011211 (200225)			

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001091536 A2		WO 2001-US18238	20010604
AU 2001071288 A		AU 2001-71288	20010604

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001071288 A	Based on	WO 200191536

PRIORITY APPLN. INFO: US 2000-585599 20000602

AB WO 200191536 A UPAB: 20020308

NOVELTY - A replication-incompetent recombinant virus (RV) comprising antigen sequences heterologous to RV, each sequence encoding a bacterial, viral or parasitic antigen whose expression elicits immune response against the antigen and cells expressing the antigen in a host upon infection of host by RV, and an immuno-stimulator (IS) sequence heterologous to RV, is new.

DETAILED DESCRIPTION - A replication-incompetent recombinant virus (RV) comprising antigen sequences heterologous to RV, each sequence encoding a bacterial, viral or parasitic antigen whose expression elicits immune response against the antigen and cells expressing the antigen in a host upon infection of host by RV, and an immuno-stimulator (IS) sequence heterologous to RV, is new. The IS sequence's expression in the host enhances the immunogenicity of the antigen, and RV does not cause a malignancy naturally associated with the pathogen in the host.

ACTIVITY - Virucide; Antibacterial; Antiparasitic; Protozoacide; Anti-HIV.

MECHANISM OF ACTION - Vaccine.

The immune responses of animals to the adenoviral vaccine against HIV antigens was studied. Experimental mice were inoculated with the adenoviral vaccine, Ad.tat.env.IL2. Groups of C57BL/6 mice were injected intramuscularly with 10⁷ plaque forming units (pfu) Ad.tat.env.IL2 on

different dates. Blood was collected from four animals every two weeks following inoculation and serum was prepared. At 77 days post-inoculation, these mice were re-challenged with an additional 107 pfu of Ad.tat.env.IL2. Blood was collected from three animals every day following secondary challenge. Titers of antibody elicited against HIV tat and env were determined by enzyme linked immunosorbent assay (ELISA) against Ad.tat.env.IL2-infected HeLa cell lysates. The results showed that three mice in this group had strong immune responses to the HIV antigens expressed by the adenoviral vector Ad.tat.env.IL2, with the highest titer of antibody against HIV antigens reached in 42 days post inoculation. The second inoculation with Ad.tat.env.IL2 boosted the immune response again and very high titers were achieved within 5 days of the second inoculation.

USE - RV is useful for enhancing the immunity of a host to one or more pathogenic bacteria such as *Bacillus tuberculosis*, *B. anthracis*, spirochete, *Borrelia burgdorferi* that causes the Lyme disease in animals, parasites such as malaria, *Cryptosporidium*, *Eimeria*, *Histomonas*, *Leucocytozoon*, *Plasmodium*, *Toxoplasma*, *Trichomonas*, *Leishmania*, *Trypanosoma*, *Giardia*, *Babesia* or *Theileria*, and pathogenic viruses such as HIV type 1 and type 2, influenza virus, respiratory syncytial virus, herpes simplex virus type 1 and type 2, human papilloma virus, Ebola virus, Marburg virus and hepatitis A, B, C, D and E virus (claimed). The host is a human.

ADVANTAGE - RV induces a strong and long-lasting immune response to various strains or types of pathogens in the host.

Dwg.0/15

L97 ANSWER 34 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2001-602931 [68] WPIDS
 CROSS REFERENCE: 2001-611723 [70]; 2001-616754 [70]; 2001-616755 [70];
 2001-616756 [70]; 2002-010886 [01]; 2002-179329 [70]
 DOC. NO. CPI: C2001-178694
 TITLE: Albumin fusion proteins comprising a therapeutic protein and albumin, useful in the treating metastatic renal cell carcinoma, metastatic melanoma, malignant melanoma, renal cell carcinoma, HIV (human immunodeficiency virus) or infection.
 DERWENT CLASS: B04 D16
 INVENTOR(S): PRIOR, C P; ROSEN, C A; SADEGHI, H; TURNER, A J
 PATENT ASSIGNEE(S): (HUMA-N) HUMAN GENOME SCI INC; (PRIN-N) PRINCIPIA PHARM CORP
 COUNTRY COUNT: 95
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001079258	A1	20011025 (200168)*	EN	325	
RW:	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW				
AU 2001059066	A	20011030 (200219)			

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001079258	A1	WO 2001-US12008	20010412
AU 2001059066	A	AU 2001-59066	20010412

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001059066 A	Based on	WO 200179258

PRIORITY APPLN. INFO: US 2000-256931P 20001221; US 2000-229358P
20000412; US 2000-199384P 20000425

AB WO 200179258 A UPAB: 20020411

NOVELTY - Albumin **fusion** proteins (P1) comprising a therapeutic protein (T1) (or its fragment or variant having the activity of T1) and albumin comprising the 585 amino acid sequence (I) defined in the specification (or its fragment or variant having albumin activity), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a kit comprising a composition containing P1;
- (2) a method of treating a disease or disorder, preferably modulated by T1, in a patient, comprising administering P1;
- (3) a method of extending the shelf-life of T1, comprising fusing T1 or its fragment or variant, to albumin or its fragment or variant, where the shelf-life of T1 or its fragment or variant as part of a fused protein is extended when compared to T1 or its fragment or variant in an unfused state;
- (4) a nucleic acid (N1) comprising a nucleotide sequence encoding P1;
- (5) a vector comprising N1; and
- (6) a host cell comprising N1.

ACTIVITY - Cytostatic; antiviral; antiinflammatory; antileukemic; antiarthritic; antirheumatic; immunosuppressive; antidiabetic; cardiant; nootropic; neuroprotective; antimicrobial; vulnerary.

To test whether sympathetic neuronal cell viability is supported by an albumin **fusion** protein, the chicken embryo neuronal survival assay (Senaldi, et al., Proc. Natl. Acad. Sci., U.S.A, 96:11458-63 (1998)). Briefly, motor and sympathetic neurons were isolated from chicken embryos, resuspended in L15 medium (with 10% fetal calf serum (FCS), glucose, sodium selenite, progesterone, conalbumin, putrescine and insulin) and Dulbecco's modified Eagles medium (with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2)), respectively and incubated at 37 degrees Centigrade in 5% carbon-dioxide in the presence of different concentrations of the purified **fusion** protein, as well as negative control lacking any cytokine. After 3 days, neuronal survival was determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mosmann, T., J. Immunol., Methods, 65:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the albumin **fusion** protein to enhance the survival of neuronal cells.

MECHANISM OF ACTION - Gene therapy.

USE - When the therapeutic protein, or its fragment or variant is IL-2, P1 is used to treat metastatic renal cell carcinoma, metastatic melanoma, malignant melanoma, renal cell carcinoma, HIV (human immunodeficiency virus) infection, inflammatory bowel disorder, Kaposi's sarcoma, leukemia, multiple sclerosis, rheumatoid arthritis, transplant rejection, type 1 diabetes mellitus, lung cancer, acute myeloid leukemia, hepatitis C, non-hodgkin's lymphoma or ovarian cancer (claimed).

The albumin **fusion** proteins are also useful in the treatment, prevention, diagnosis, and/or detection of diseases, disorders such as immune system disorders (e.g. transplant rejection), blood related disorders (e.g. myocardial infarction), hyperproliferative disorders (e.g. childhood acute myeloid leukemia), renal disorders (e.g. glomerulonephritis), cardiovascular disorders (e.g. arrhythmias), respiratory disorders (e.g. non-allergic rhinitis), neurological diseases (e.g. Alzheimer's disease), endocrine disorders (e.g. pheochromocytoma), reproductive system disorders (e.g. syphilis), infectious diseases (e.g. measles), gastrointestinal disorders (e.g. irritable bowel syndrome) and

wound healing.
Dwg. 0/14

L97 ANSWER 35 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2001-123319 [13] WPIDS
 DOC. NO. CPI: C2001-035888
 TITLE: Immunogenic compositions comprising Flt-3 ligand encoding polynucleotide and one or more antigen, or cytokine encoding polynucleotides, useful for suppressing tumor growth and for treating autoimmune diseases (e.g. rheumatoid arthritis).
 DERWENT CLASS: B04 D16
 INVENTOR(S): HERMANSON, G G
 PATENT ASSIGNEE(S): (VICA-N) VICAL INC
 COUNTRY COUNT: 21
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001009303	A2	20010208 (200113)*	EN	149	
RW:	AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE				
W:	CA JP US				

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001009303	A2	WO 2000-US20679	20000731

PRIORITY APPLN. INFO: US 1999-146170P 19990730

AB WO 200109303 A UPAB: 20010307

NOVELTY - Immunogenic compositions comprising Flt-3 ligand encoding polynucleotide and one or more antigen or cytokine encoding polynucleotides, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are provided for:

(1) a composition (C1) comprising:

(a) 1 ng to 10 mg of a nucleic acid comprising a first polynucleotide (N1) which hybridizes, at 42 deg. C in 50% formamide, 5 x SSC (saline sodium chloride), 50 mM sodium phosphate, 5 x Denhardt's solution, 10% dextran sulfate, and 20 micro g/ml denatured, sheared salmon sperm DNA, followed by washing at 65 deg. C in 0. 1 x SSC and 0. 1 % sodium dodecyl sulfate (SDS) (w/v), to a reference nucleic acid having a 839, 852, 1152, 663, 519, 1080, 537, or 859 (S1-S8, respectively) nucleotide sequence defined in the specification, or their complements, where the first polynucleotide encodes a polypeptide having immunity-enhancing activity when administered to a vertebrate;

(b) 1 ng to 30 mg of a nucleic acid (N2) comprising a second polynucleotide encoding one or more antigens, or one or more cytokines, where the first and second polynucleotides are non-infectious and non-integrating, and are operably associated with control sequences which direct their expression;

(2) a composition (C2) comprising:

(a) 1 ng to 10 mg of a nucleic acid comprising a first polynucleotide (N3) which encodes a first polypeptide which, except for at least one but not more than 20 amino acid substitutions, deletions, or insertions, is identical to a second polypeptide selected from amino acids 28 to 163 of the 231 amino acid sequence (S9), amino acids 27 to 160 of 235 amino acid sequence (S15), or amino acids 27 to 185 of 235 amino acid sequence (S17) (all sequences are defined in the specification), where the first polypeptide has immunity-enhancing activity when administered to a vertebrate;

(b) 1 ng to 30 mg of N2, where the first and second polynucleotides

are non-infectious and non-integrating, and are operably associated with control sequences which direct their expression;

(3) a pharmaceutical composition (C3) comprising:

(a) 1 ng to 10 mg of a nucleic acid molecule comprising a first polynucleotide (N4) encoding an amino acid sequence that is at least 90%, preferably 97%, identical to a reference amino acid sequence selected from S9, 189 (S10), 220 (S11), 232 (S12), 172 (S14), S15, 178 (S16), S17 or 185 (S18) amino acid sequence defined in the specification, where % identity is determined using the Bestfit program with default parameters, and the polypeptide has immunity-enhancing activity when administered to a vertebrate;

(b) 1 ng to 30 mg of N2, where the first and second polynucleotides are non-infectious and non-integrating, and are operably associated with control sequences which direct their expression;

(4) a method (M1) for enhancing an immune response in a vertebrate, comprising administering C1, C2 or C3 to a tissue of the vertebrate, where the first and second polynucleotides are expressed in vivo in an amount effective for a polypeptide expressed by the first polynucleotide to enhance the immunogenicity of one or more antigens, or one or more cytokines; and

(5) a method (M2) of suppressing tumor growth in a mammal, comprising administering C1, C2 or C3 to a tissue of a mammal.

ACTIVITY - Antirheumatic; antiarthritic; immunostimulant; antiviral; antibacterial; antifungal; antiparasitic; cytostatic; immunosuppressive; protozoacide; antiinflammatory.

Three groups of mice were used in the study. One group (n=9) was co-injected with VR6200 (a Flt-3 ligand-encoding plasmid) and VR1623 (bicistronic chimeric Id vector) (100 micro g each) on days 0, 14, and 28, and challenged with 500 38C13 tumor cells two weeks following the last injection. Control groups (n=10 each) were co-injected with VR1623 and VR1051 (control plasmid), or VR1605 (generic cloning vector comprising the constant regions of human kappa light chain and gamma 1 heavy chain separated by a CITE (cap independent translational enhancer)) or alone (200 micro g) on days 0, 14, and 28, and challenged with 500 38C13 tumor cells two weeks following the last injection.

The co-injection of a Flt-3 ligand-encoding plasmid (100 micro g of VR6200) with a tumor-specific antigen-encoding plasmid (100 micro g of VR1623) significantly enhanced protection from tumor challenge. Eight out of nine mice injected with VR1623 and VR6200 survived the challenge as compared to zero out of ten mice surviving after being immunized with VR1623 and the control plasmid, VR1051. This increased survival was statistically significant p=0.00007. Furthermore, the co-injection of a Flt-3 ligand-encoding plasmid (VR6200) with an idiotype antigen-encoding plasmid (VR1623) resulted in greatly enhanced anti-Id antibody titer relative to mice injected with VR1623 and VR1051, or with VR1623 alone.

MECHANISM OF ACTION - Vaccine.

USE - The compositions are useful for suppressing tumor growth in a mammal. The tumor is melanoma, glioma or lymphoma, particularly B-cell lymphoma. The compositions are used in conjunction with additional cancer treatments (claimed).

The immunogenic compositions can also be used for the prophylactic and/or therapeutic treatment of:

(a) bacterial (e.g. *Bacillus* infections), viral (e.g. hepatitis B and C in humans), parasitic (e.g. malaria) and fungal infections;

(b) autoimmune diseases (e.g. rheumatoid arthritis and osteoarthritis);

(c) cancer (e.g. cancers of stomach, small intestine, liver, etc.); and

(d) Aujeszky's disease in pigs.

Various other examples of these diseases are given in the specification.

Dwg.0/9

L97 ANSWER 36 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2000-339534 [29] WPIDS
 DOC. NO. CPI: C2000-103004
 TITLE: New **glycosylated interferon-beta-1a** coupled to a non-naturally occurring polymer containing a **polyalkylene glycol** useful for treating e.g. tumors, autoimmune disorders, viral infections and angiogenic diseases.
 DERWENT CLASS: A25 A96 B04
 INVENTOR(S): BRICKELMAIER, M; HOCHMAN, P S; PEPINSKY, B; RUNKEL, L; WHITTY, A; HOCHMAN, P
 PATENT ASSIGNEE(S): (BIOJ) BIOGEN INC
 COUNTRY COUNT: 89
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
<hr/>					
WO 2000023114	A2	20000427 (200029)*	EN	71	
RW:	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW				
W:	AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW				
AU 2000014465	A	20000508 (200037)			
NO 2001001860	A	20010615 (200141)			
EP 1121156	A2	20010808 (200146)	EN		
R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI				
BR 9915542	A	20010814 (200154)			
CZ 2001001329	A3	20010912 (200158)			
SK 2001000506	A3	20020107 (200213)			
CN 1323225	A	20011121 (200218)			
KR 2001103605	A	20011123 (200232)			

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000023114	A2	WO 1999-US24201	19991015
AU 2000014465	A	AU 2000-14465	19991015
NO 2001001860	A	WO 1999-US24201	19991015
		NO 2001-1860	20010411
EP 1121156	A2	EP 1999-970609	19991015
		WO 1999-US24201	19991015
BR 9915542	A	BR 1999-15542	19991015
		WO 1999-US24201	19991015
CZ 2001001329	A3	WO 1999-US24201	19991015
		CZ 2001-1329	19991015
SK 2001000506	A3	WO 1999-US24201	19991015
		SK 2001-506	19991015
CN 1323225	A	CN 1999-812202	19991015
KR 2001103605	A	KR 2001-704800	20010416

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000014465	A Based on	WO 200023114
EP 1121156	A2 Based on	WO 200023114
BR 9915542	A Based on	WO 200023114
CZ 2001001329	A3 Based on	WO 200023114

SK 2001000506 A3 Based on

WO 200023114

PRIORITY APPLN. INFO: US 1999-120161P 19990216; US 1998-104572P
19981016

AB WO 200023114 A UPAB: 20000617

NOVELTY - A composition comprising a **glycosylated interferon- beta** coupled to a non-naturally-occurring polymer containing a **polyalkylene glycol**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a physiologically active **interferon (IFN)-beta** composition, comprising a physiologically active IFN- beta 1a coupled to a polymer comprising a **polyalkylene glycol** moiety, and arranged so that the composition has enhanced activity, measured by an antiviral assay, as compared to physiologically active IFN-beta ;

(2) a physiologically active IFN- beta composition, comprising a physiologically active **glycosylated IFN- beta N-terminally** coupled to a polymer comprising a **polyalkylene glycol** moiety and arranged so that the composition has enhanced activity, measured by an antiviral assay, as compared to physiologically active IFN-beta ;

(3) a stable, aqueously soluble, conjugated **interferon-beta-1a** complex comprising an IFN- beta 1a coupled to a polyethylene glycol moiety by a labile bond, where the labile bond is cleavable by biochemical hydrolysis and /or proteolysis;

(4) a pharmaceutical composition, comprising the novel composition, or the composition of (1) or (2);

(5) a method of treating a potential or developed condition or disease state in a mammalian subject with a **interferon-beta-1a** effective therefore, comprising administering a composition comprising the IFN- beta 1a coupled to a polyethylene glycol moiety;

(6) a method of prolonging the activity of IFN- beta 1a in an in vivo or in vitro system comprising coupling the **interferon-beta 1a** to a non-naturally occurring polymer moiety to yield a coupled polymer-IFN- beta 1a composition, and introducing the coupled polymer-IFN- beta composition to the in vivo or in vitro system; and

(7) a method of inhibiting angiogenesis in a subject, comprising administering an **interferon-beta** composition.

ACTIVITY - Cytostatic; immunosuppressive; antiviral; antidiabetic; ophthalmological; antiinflammatory; neuroprotective.

MECHANISM OF ACTION - Cell proliferation inhibitor; gene therapy.

USE - The polymer-based conjugates are useful for treating tumors and cancer such as osteogenic sarcoma, lymphoma, acute lymphocytic leukemia, breast carcinoma, melanoma and nasopharyngeal carcinoma, as well as autoimmune conditions such as fibrosis, lupus and multiple sclerosis. These may also be used in the treatment of viral diseases such as ECM infection, influenza and other respiratory tract infections, rabies, and hepatitis, as well as in the treatment of angiogenic diseases such as diabetic retinopathy, retinopathy of prematurity, muscular degeneration, corneal graft rejection, neovascular glaucoma, retrothalamic fibroplasia, rubeosis, and Osler Webber syndrome. IFN- beta 1a is useful as an agent for the treatment, remission or attenuation of a disease state, physiological condition, symptoms or etiological factors, or for their evaluation or diagnosis. The new IFN- beta 1a polymer conjugates may also be used for prophylaxis or treatment of any condition or disease state for which the IFN- beta 1a constituent is efficacious, in biological systems or specimens, as well as in non-physiological systems.

ADVANTAGE - The polymer-IFN- beta 1a conjugate has the ability to stay in the vasculature for longer periods of time, has increased stability in solution, reduced immunogenicity, protection of the modified

interferon-beta-1a from proteolytic digestion and subsequent abolition activity, and increased thermal stability which can lead to more effective formulation of powdered IFN- beta 1a for oral or inhaled use.

Dwg.0/10

L97 ANSWER 37 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2000-194968 [17] WPIDS
 DOC. NO. CPI: C2000-060376
 TITLE: Use of inhibitor of interaction of glutamate with alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate or kainate receptor complex for treatment of demyelinating disorders e.g. multiple sclerosis.
 DERWENT CLASS: B05
 INVENTOR(S): SMITH, T; TURSKI, L
 PATENT ASSIGNEE(S): (EISA) EISAI CO LTD
 COUNTRY COUNT: 21
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000001376	A2	20000113	(200017)*	EN	104
RW:	AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE				
W:	JP US				
EP 1100504	A2	20010523	(200130)	EN	
R:	AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE				

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000001376	A2	WO 1999-GB2112	19990702
EP 1100504	A2	EP 1999-929545	19990702
		WO 1999-GB2112	19990702

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1100504	A2 Based on	WO 200001376

PRIORITY APPLN. INFO: GB 1998-24393 19981106; GB 1998-14380 19980702

AB WO 200001376 A UPAB: 20000405
 NOVELTY - Use of an inhibitor (I) of the interaction of glutamate with the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptor complex and of the interaction of glutamate with the kainate receptor complex in the manufacture of a medicament for treatment of demyelinating disorder (DMD) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
 (1) use of an inhibitor of interaction of glutamate with an AMPA receptor for treatment of demyelinating disorders;
 (2) use of an inhibitor of interaction of glutamate with the kainate receptor for treatment of demyelinating disorders.

ACTIVITY - Neuroprotective; immunosuppressive.
 The figure shows the effect of the AMPA receptor antagonist NBQX on severity of paralysis during experimental allergic encephalomyelitis (EAE) in rats, at a dose of 30 mg/kg twice daily.

MECHANISM OF ACTION - Glutamate-AMPA and/or kainate receptor complex interaction inhibitors.

USE - For treatment of DMD such as acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple

sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, human immunodeficiency virus (HIV)- or human T-cell leukemia virus (HTLV)-myelopathy, progressive multifocal leucoencephalopathy or a secondary demyelinating disorder, particularly central nervous system (CNS) lupus erythematoses, polyarteritis nodosa, Sjogren syndrome, sarcoidosis or isolated cerebral vasculitis (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows the effect of the AMPA receptor antagonist NBQX on severity of paralysis during EAE in rats, at a dose of 30 mg/kg twice daily.

Dwg.1/8

L97 ANSWER 38 OF 38 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 1985-304732 [49] WPIDS
 DOC. NO. CPI: C1985-131672
 TITLE: Human T and B cells contg. Ela human adenovirus gene -
 able spontaneously to produce immunologically active
 cpds., e.g. interferon or interleukin.
 DERWENT CLASS: B04 D16
 INVENTOR(S): MORIOKA, H; ONODERA, K; SHIBAI, H
 PATENT ASSIGNEE(S): (AJIN) AJINOMOTO KK
 COUNTRY COUNT: 9
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 163243	A	19851204 (198549)*	EN	29	
R: AT CH DE FR GB IT LI					
JP 60248177	A	19851207 (198604)			
US 4758513	A	19880719 (198831)			

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 60248177	A	JP 1984-102282	19840521
US 4758513	A	US 1985-736376	19850521

PRIORITY APPLN. INFO: JP 1984-102282 19840521

AB EP 163243 A UPAB: 19930925

A human T or B cell contains at least one Ela human adenovirus 12-type gene (or fragment) and is able to spontaneously produce immunologically active substances (A). (A) is esp. alpha, beta or gamma interferons, interleukins 1 or 2; B cell growth factor, or CSF. Also claimed is prodn. of (A) by culturing these new cells.

The T and B cells can be normal or malignant, esp. they are from leukaemic patients, virus-transformed cells; drug- or radiation-transformer cells, or fusion prods. of normal T cells with myeloma or malignant T cells.

ADVANTAGE - These cells produce (A) very efficiently without any need for stimulation by inducers.

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